

# Ephedrine Increases Ventricular Arrhythmias in Conscious Dogs After Myocardial Infarction

Philip B. Adamson, MD, FACC,\*† Jennifer Suarez, BS,\* Ethannah Ellis, BS,\* Travis Kanaly, BS,\* Emilio Vanoli, MD\*†‡

Oklahoma City, Oklahoma; and Pavia, Italy

<b>OBJECTIVES</b>	This study examined the hypothesis that the sympathomimetic activity of ephedrine increases the risk of lethal arrhythmias.
<b>BACKGROUND</b>	The sympathomimetic amine, ephedrine, is used to augment physical performance and as a weight loss aid, but little is known about the cardiovascular consequences in individuals with ischemic heart disease.
<b>METHODS</b>	Fifteen dogs at low risk for ventricular fibrillation (VF) during exercise and transient myocardial ischemia 30 days after a small anterior myocardial infarction were retested after five days of ephedrine use (Xenadrine, 0.4 mg/kg/day orally). To assess the effects of ephedrine on cardiac autonomic control, baroreceptor reflex sensitivity (BRS), heart rate (HR) variability, HR response to acute myocardial ischemia, and resting catecholamines were measured before and after ephedrine. Dogs were used as their own control when possible.
<b>RESULTS</b>	Nine of 15 animals had increased ventricular arrhythmias during ephedrine treatment ( $p = 0.01$ ) and four had VF. Three dogs that had VF could not be resuscitated. Five animals with increased arrhythmias during ephedrine treatment had none during a third exercise and ischemia test after drug washout. Heart rates were higher after 30 s of myocardial ischemia during ephedrine treatment ( $204 \pm 25$ beats/min no drug vs. $218 \pm 26$ beats/min with ephedrine, $p = 0.03$ ). All plasma catecholamines increased after ephedrine administration. No changes in BRS, HR variability, or exercise HR were noted.
<b>CONCLUSIONS</b>	Ephedrine increases ischemia-dependent arrhythmias at doses recommended in over-the-counter preparations. Increased arrhythmia risk was associated with augmented ischemia-dependent sympathetic reflex activation. (J Am Coll Cardiol 2004;44:1675–8) © 2004 by the American College of Cardiology Foundation

Use of over-the-counter sympathomimetic amines, intended to augment physical performance in athletes or as a weight loss aid, is controversial, and there is little information on potential risks (1). Cardiovascular symptoms comprise almost one-half of the adverse events reported to the U.S. Food and Drug Administration (FDA) (2) and range from cerebrovascular accidents to seizures and ventricular fibrillation (VF) (2). Recently, the U.S. FDA banned the sale of ephedrine-containing supplements (3), based on growing concerns about the adverse health effects of the compound when made available without physician supervision. However, systematic data on the cardiovascular effects of ephedrine and, specifically, any potential arrhythmogenic effects are not available.

Sympathetic activation, as may occur with ephedrine use, may alter cardiac electrophysiology leading to an arrhythmogenic trigger (4) in individuals with cardiac disease, even if they are at relatively low arrhythmia risk. Even higher risk of adverse cardiovascular events may occur in subjects with ischemic heart disease. Therefore, autonomic alterations may be the underlying mechanism for the sudden cardiac deaths associated with ephedrine use in case reports. This

study examined the hypothesis that ephedrine supplements, used in doses recommended in over-the-counter preparations, increase the relative risk of ischemia-dependent ventricular arrhythmias in the presence of chronic ischemic heart disease. This hypothesis was tested using a clinically relevant canine model of sudden death in which two reproducible populations of animals are produced, based on their relative risk of VF during exercise and transient myocardial ischemia 30 days after myocardial infarction (MI) (5–8).

## METHODS

**Surgical instrumentation.** Healthy mongrel dogs (weight 18 to 25 kg) were used for this study, and protocols for surgical instrumentation have been published (6–8). Briefly, during general anesthesia, an anterior MI was created by a two-stage permanent ligation of the left anterior descending coronary artery. Pacing leads were secured to the right atrium and ventricle, and a pneumatic vascular occluder and 20-MHz Doppler blood flow probe were implanted around the left circumflex coronary artery. A catheter was placed in the descending aorta for later evaluation of arterial pressures. Instrumentation was exteriorized at the dorsum of the neck.

Postoperative care was administered in a special high-oxygen-flow intensive care cage, and each dog immediately received a short-acting analgesic (pentazocine lactate,

From the \*Department of Physiology, †Department of Medicine, Cardiovascular Diseases, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; and ‡Dipartimento di Cardiologia, Policlinico San Matteo, IRCCS e Università di Pavia, Pavia, Italy.

Manuscript received June 2, 2004; revised manuscript received July 15, 2004, accepted July 20, 2004.

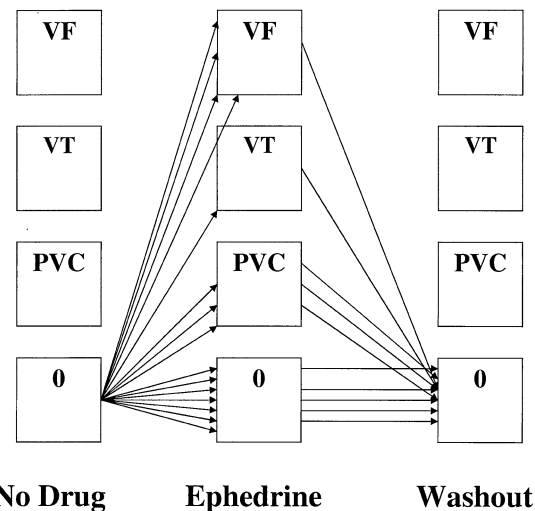
#### Abbreviations and Acronyms

BRS	=	baroreflex sensitivity
FDA	=	Food and Drug Administration
HR	=	heart rate
MI	=	myocardial infarction
VF	=	ventricular fibrillation

1 mg/kg intramuscularly), followed by a longer acting agent (nubain, 1 mg/kg intramuscularly). Dogs were allowed to recover for 30 days before any further experimentation. The local Institutional Animal Care and Use Committee reviewed and approved all protocols. Guidelines on the use of animals in long-term research, as outlined by the U.S. National Institutes of Health, American Physiologic Society, and American Heart Association, were strictly followed. **Risk assessment for VF.** After recovery from the acute MI and daily acclimation to the laboratory, each dog's risk of VF was evaluated using a submaximal exercise test coupled with transient myocardial ischemia, according to previously published methods (6-8). Dogs ran on a motorized treadmill starting at 3 mph at 0% incline and increasing every 3 min up to 4 mph at 12% incline, until the heart rate (HR) reached a target range of 210 beats/min. At the target HR, the circumflex occluder was inflated for 2 min; dogs continued to run for the first minute, and the treadmill was stopped for the second minute.

Dogs that developed VF during the 2 min of transient myocardial ischemia were allowed to lose consciousness and were then defibrillated. These dogs were labeled as "susceptible" to sudden death. Dogs that did not develop VF were labeled as "resistant" to sudden death. Arrhythmia risk status was always confirmed with a second no-drug exercise and ischemia test documenting the initial risk status before the animal entered the drug protocol. Only resistant dogs entered the study and were tested again to study the potential pro-arrhythmic effect of ephedrine using internal control analysis. Two investigators (Drs. Adamson and Vanoli) reviewed digitized electrocardiographic recordings from the entire 2 min of myocardial ischemia to determine the incidence of ventricular arrhythmias, while blinded to treatment status. Ventricular ectopy was classified as isolated premature ventricular contractions (1 to 3 successive ventricular contractions), ventricular tachycardia (>3 successive ventricular contractions), and VF. A final exercise and ischemia test was performed in surviving animals after drug washout.

**Drug testing.** Ephedrine (Xenadrine RFA-1; CYTODYNE Technologies, Lakewood, New Jersey) was purchased over the counter from a local health food store. Each capsule contained 10 mg ephedrine, and dosing in this study followed the labeling instructions provided with the product. The maximum dose recommended was 100 mg/day for a healthy adult, not to exceed 12 weeks. Initial recommended therapy was for 10 mg twice daily (total 20 mg/day) and increased to 20 mg twice daily after one week in conjunction with physical workouts.



**Figure 1.** Arrhythmia incidence during no-drug control (left), ephedrine treatment (middle), and drug washout (right). The 60% increase in arrhythmia incidence during ephedrine therapy was significant ( $p < 0.02$ ). PVC = premature ventricular contractions; VF = ventricular fibrillation; VT = ventricular tachycardia.

Assuming a human weight of 80 kg, the maintenance dose equates to 0.5 mg/kg/day. The dose chosen in this study was 0.4 mg/kg/day in divided doses for five days.

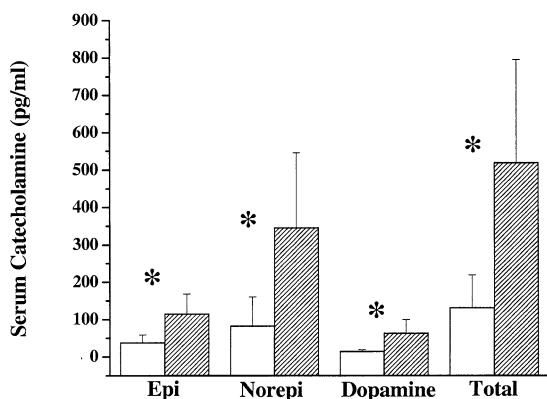
**Autonomic testing.** Baroreflex sensitivity (BRS) was measured in the first 10 dogs tested while the animals were resting comfortably on a padded table. The blood pressure rise in response to phenylephrine bolus (2 to 3  $\mu$ g/kg intravenously) was correlated to the RR-interval slowing, and a regression line was computed. The slope of the regression line defined BRS, and only significant correlations ( $R > 90\%$ ) were used. Testing was performed at baseline and after five days of ephedrine use.

Serum catecholamine levels were obtained from blood drawn while the animals were resting comfortably on a padded table. Catecholamine levels were measured by the clinical laboratories at the University of Oklahoma Health Sciences Center.

**Statistical analysis.** A change in arrhythmia incidence was defined as the development of premature ventricular contractions, ventricular tachycardia, or VF during the 2 min of transient myocardial ischemia. The significance of arrhythmia incidence was examined using the chi-square test. Changes in cardiovascular parameters were tested using the Student *t* test for paired observations. An alpha level of  $p < 0.05$  was considered significant. Data are presented as the mean value  $\pm$  SD, unless otherwise noted.

## RESULTS

**Risk of VF.** No dog had ventricular ectopy during the initial exercise and myocardial ischemia test. Nine of the 15 resistant dogs studied had increased ventricular arrhythmias during the exercise and ischemia test performed after five days of ephedrine therapy ( $p = 0.01$ ) and four of those developed VF (Fig. 1). Only one animal that developed VF



**Figure 2.** Serum catecholamine levels before (no drug; open bars) and after treatment with ephedrine (hatched bars). Epi = epinephrine; Norepi = norepinephrine; Total = total catecholamines. \* $p < 0.001$ .

during the ephedrine test was successfully resuscitated. None of the surviving animals had ventricular arrhythmias when re-tested after ephedrine washout.

In the no-drug exercise and myocardial ischemia test, HRs averaged  $199 \pm 23$  beats/min at the onset of circumflex occlusion and increased slightly after 30 s of myocardial ischemia to  $204 \pm 25$  beats/min ( $p > 0.1$ ), reflecting the typical pattern of autonomic response to ischemia of resistant dogs. After ephedrine, HRs immediately before coronary occlusion were  $188 \pm 38$  beats/min ( $p = \text{NS}$  vs. no-drug) and increased to  $218 \pm 26$  beats/min after 30 s of occlusion ( $p = 0.03$  vs. no-drug test). Ephedrine use did not change BRS measurements ( $21 \pm 10$  ms/mm Hg control vs.  $17 \pm 9$  ms/mm Hg after ephedrine,  $p = 0.1$ ). Corrected QT intervals, measured while the animals were standing on the treadmill immediately before the onset of exercise, were  $292 \pm 40$  ms in no-drug conditions and  $288 \pm 14$  ms after ephedrine.

Serum catecholamines increased after ephedrine dosing, as demonstrated in Figure 2. Most of the change in catecholamines was accounted for by a fourfold increase in norepinephrine (from  $81.9 \pm 78.3$  pg/ml [no-drug] to  $345 \pm 200$  pg/ml,  $p < 0.0001$ ).

## DISCUSSION

This study demonstrates that ephedrine increases the risk of ischemia-dependent ventricular arrhythmias in the presence of chronic ischemic heart disease. The data also provide meaningful insights regarding ephedrine's cardiovascular effects, which have not been assessed in clinical trials. First, at recommended doses, ephedrine did not change the HR response to graded exercise in subjects with a healed MI, but it augmented the HR response to acute myocardial ischemia. There was also limited clinical evidence in normal obese persons (9) of an exercise HR effect, but no data are available in subjects with overt coronary disease. Heart rates after 30 s of coronary occlusion were significantly higher in resistant dogs taking ephedrine, but did not increase to levels characteristic of susceptible dogs (7).

The mechanisms involved in the tachycardia response to acute ischemia are primarily determined by acute activation of sympathetic afferents resulting in decreased vagal and increased sympathetic cardiac efferent activity (10). Ephedrine administration resulted in a four-fold increase in circulating norepinephrine levels, suggesting that neural sympathetic outflow was augmented. Because most of the HR response to moderate exercise is mediated by vagal withdrawal (11), it is not surprising that the HRs during exercise in this and other studies were unaffected by ephedrine. However, when sympathetic reflexes were activated by transient myocardial ischemia, the cardio-acceleration was significantly augmented by ephedrine's effect on sympathetic outflow. In this situation, ischemia-dependent arrhythmias were more likely to occur.

No previous animal studies testing potential pro-arrhythmia with ephedrine are available, but a significant volume of data are available documenting the fact that cardiac sympathetic activation increases the risk of sudden death (4–8,12–14). Anecdotal reports to the U.S. FDA are available, suggesting that cardiovascular events account for almost one-half of the adverse events reported with ephedrine (2), but the true incidence of cardiovascular complications cannot be determined from case reports alone. A longitudinal clinical trial designed to assess the safety of ephedrine-containing supplements would require large numbers of subjects and will not likely occur.

Data from the present study may help this deficit in evidence by predicting that individuals with clinical or subclinical ischemic heart disease are at high risk of ventricular arrhythmias and sudden death during treatment with ephedrine. The animal model used in this study is known to have clinical relevance for examining the mechanisms of sudden death (6). Cardiac autonomic assessment with BRS and HR variability, to predict sudden death risk, was first described in this model (7) and subsequently clinically validated (14). Furthermore, interventions that prevent VF in this model, such as beta-blockers, sympathectomy, amiodarone, and *d,l*-sotalol, effectively reduce arrhythmic mortality in clinical populations (6). Finally, interventions that do not prevent VF in this model are ineffective in clinical populations, such as dofetilide, azimilide, and *d*-sotalol (6).

**Conclusions.** Ephedrine use in animals with chronic ischemic heart disease is associated with an increased risk of ventricular arrhythmias during acute ischemic events. The experimental setting used in this study portrays a complex condition of acute ischemia coupled with a healed MI. However, the 60% increase in ventricular arrhythmias in the low-risk animals used in this study creates a strong warning for less severe conditions, specifically considering the widespread incidence of asymptomatic coronary artery disease. This is important, because up to 44% of sudden deaths are the first manifestation of ischemic heart disease (15).

**Reprint requests and correspondence:** Dr. Philip B. Adamson, University of Oklahoma Health Sciences Center, Department of Medicine, Cardiovascular Diseases Section, 920 S. L. Young Blvd, WP3120, Oklahoma City, Oklahoma 73190. E-mail: Philip-adamson@ouhsc.edu.

## REFERENCES

1. Pipe A, Ayotte C. Nutritional supplements and doping. *Clin J Sport Med* 2002;12:245-9.
2. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;343:1833-8.
3. Rados C. Ephedra ban: no shortage of reasons. *FDA Consum* 2004;38:6-7.
4. Schwartz PJ. Another role for the sympathetic nervous system in the long QT syndrome? *J Cardiovasc Electrophysiol* 2001;12:500-2.
5. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death: experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992;85 Suppl I:I77-91.
6. Schwartz PJ. Do animal models have clinical value? *Am J Cardiol* 1998;81:14D-20D.
7. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with a healed myocardial infarction: an experimental preparation for sudden cardiac death. *Circulation* 1984;69:780-90.
8. Adamson PB, Huang MH, Vanoli E, et al. Unexpected interaction between beta-adrenergic blockade and heart rate variability before and after myocardial infarction: a longitudinal study in dogs at high and low risk for sudden death. *Circulation* 1994;90:976-82.
9. Kalman D, Incledon T, Gaunard I, et al. An acute clinical trial evaluating the cardiovascular effects of an herbal ephedra-caffeine weight loss product in healthy overweight adults. *Int J Obes Relat Metab Disord* 2002;26:1363-6.
10. Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. *Am J Physiol* 1969;217:703-9.
11. Rowell LB, O'Leary DS. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol* 1990;69:407-18.
12. Swissa M, Zhou S, Gonzalez-Gomez I, et al. Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death. *J Am Coll Cardiol* 2004;43:858-64.
13. Chen PS, Chen LS, Cao JM, et al. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res* 2001;50:409-16.
14. La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation* 2001;103:2072-7.
15. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol* 1997;30:1500-5.